nucleotides and preferably 9-21 complementary nucleotides for hybridization (last sentence, p. 23). The specification also indicates that short probes are advantageous for discrimination and longer probes for signal intensity, and that it can be advantageous to include different probe lengths on the same chip (p. 24). The specification also indicates that many probe lengths can be tested for suitability simultaneously using an optimization block (p. 25, second paragraph). The Examiner provides no comment on all of this guidance or other explanation why given this guidance the skilled person would be unable to select probes of a suitable length without undue experimentation.

With respect to reference sequence, the specification indicates that any polynucleotide of known sequence can serve as a reference sequence (p. 15, lines 11-12). Thus, the length of the reference sequence is not critical to the claimed invention. The Examiner has not explained why undue experimentation would be required in selecting a suitable reference sequence given that virtually any sequence could be used.

11. A Claims 82-92 stand rejected under 35 USC 112, second paragraph for alleged omission of essential elements, these being the probe length and information regarding the reference sequence.

As previously discussed, the claims already inherently require that the array include probes of sufficient length to hybridize to the target sequence. It is not clear what other information, the Examiner is alleging is essential. If the Examiner is suggesting that the claims should recite a specific numerical range of lengths, the Examiner has not pointed to any teaching in the specification or elsewhere that such a range is essential. On the contrary, as indicated above, the specification indicates that shorter probes are advantageous for discrimination and longer probes for signal intensity, and that the optimal length of probes may vary somewhat depending on the target sequence being read.

With respect to the reference sequence, the claims already specific that it comprises a predetermined sequence of nucleotides. As noted above, the specification teaches all such references are suitable. The Examiner has not identified what other

information about the reference sequence is essential or where such teaching is found in the specification.

In the interests of compact prosecution, applicants have attempted to address the substance of the Examiner's remarks. Nevertheless, it is noted that the rejection appears to have been brought under the wrong statutory basis. The Examiner's complaint that essential elements have been omitted is listed as a ground for rejection under 35 USC §112, first paragraph under the first clause of MPEP 2172.01, but is not listed as a ground for rejection under 35 USC 112, second paragraph under the second clause of MPEP.[1] Thus, clarification of the statutory basis of the rejection is requested if the rejection is maintained.

Further, both clauses of MPEP 2172.01 "essential elements" of the invention are those defined as such in the specification or from other statements of record. The Examiner has not pointed to any statement in the application or the record to justify her position that an essential step has been omitted. Thus, if the rejection is maintained Applicants request the Examiner indicate with specificity where in the application or record she is replying on for statements by applicants that on omitted element is essential. However, for the reasons given above, it is submitted that no essential steps have been omitted and the rejection should be withdrawn.

B. Claim 82 stands rejected on the basis that the claim does not specify how to determine whether a nucleotide in the target sequence is the same or different from a corresponding nucleotide in the reference sequence. This rejection is respectfully traversed.

The claim, as phrased, is intended to be generic to multiple methods of determining how a nucleotide in the target sequence is the same or different from a

---

[1] MPEP 2172.01 has two clauses. The first clause states that a "claim which omits matter disclosed to be essential to the invention as described in the specification or other statements of record may be rejected under 35 USC 112, first paragraph, as not enabling." The second clause states that a "claim which fails to interrelate essential elements of the invention as defined by the applicant(s) in the specification may be rejected under 35 USC 112, second paragraph."

corresponding nucleotide in a reference sequence. Two different methods are recited in the two following claims. Given these two different methods of determining, it is apparent that no single method is essential to the practice of the invention. Thus, a generic claim is appropriate.

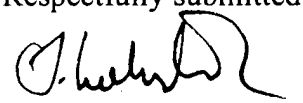
Applicants also note, for the reasons given above, that it appears that the rejection is brought under the wrong statutory section, and does not point to any statements in the specification or record that support the Examiner's position that a particular method of determining is essential to the invention.

C-E. The term "segment" has been deleted from the claims.

12-15. Applicants provide a terminal disclaimer over US 5,837,832, 6,027,880 and 6,309,823. The Examiner's attention is also drawn to USSN 08/510,521 and 09/798,260 containing related subject matter. However since neither of these applications has been allowed, it is submitted that a terminal disclaimer is not required.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

On page 9, at lines 30-34, replace the paragraph with the following:

-- Fig. 1: Basic tiling strategy. The figure illustrates the relationship between an interrogation position (I) and a corresponding nucleotide (n) in the reference sequence (SEQ. ID. No. 192), and between a probe from the first probe set and corresponding probes from second, third and fourth probe sets.--

On page 9, at line 35-36, replace the paragraph with the following:

-- Fig. 2: Segment of complementarity in a probe from the first probe set (SEQ. ID. No. 193).--

On page 9, at line 37 to page 10, line 4, replace the paragraph with the following:

--Fig. 3: Incremental succession of probes in a basic tiling strategy. The figure shows four probe sets, each having three probes (SEQ. ID. Nos. 195-206). Note that each probe differs from its predecessor in the same set by the acquisition of a 5' nucleotide and the loss of a 3' nucleotide, as well as in the nucleotide occupying the interrogation position (SEQ. ID. No. 194).--

On page 10, line 13 and 14, replace the paragraph with the following:

--Fig. 4C: A tiling strategy for avoiding loss of signal due to probe self-annealing. The reference sequence is (SEQ. ID. No. 207).--

On page 10, line 15 through line 19, replace the paragraph with the following:

--Fig. 5: Hybridization pattern of chip having probes laid down in lanes. Dark patches indicate hybridization. The probes in the lower part of the figure (SEQ. ID. Nos. 210-213) occur at the column of the array indicated by the arrow when the probes length is 15 and the interrogation position 7. The reference sequences are (SEQ. ID. Nos. 208-209).--

On page 10, line 28 through line 31, replace the paragraph with the following:

--Fig. 9: Helper mutation strategy. The segment of complementarity differs from the complement of the reference sequence (SEQ. ID. No. 214) at a helper mutation as well as the interrogation position.--

On page 10, line 32 through page 11, line 6, replace the paragraph with the following:

--Fig. 10: Block tiling array of probes for analyzing a CFTR point mutation. Each probe shown actually represents four probes, with one probe having each of A, C, G or T at the interrogation position N. In the order shown, the first probe shown on the left is tiled from the wildtype reference sequence (SEQ. ID. No. 215), the second probe from the mutant sequence (SEQ. ID. No. 216), and so on in alternating fashion. Note that all of the probes are identical except at the interrogation position, which shifts one position between successive probes tiled from the same reference sequence (e.g., the first, third and fifth probes in the left hand column.) The grid shows the hybridization intensities when the array is hybridized to the reference sequence.--

On page 11, lines 11-16, replace the paragraph with the following:

--Fig. 12, in panels A, B, and C, shows an image made from the region of a DNA chip containing CFTR exon 10 probes; in panel A, the chip was hybridized to a wild-type target; in panel C, the chip was hybridized to a mutant ΔF508 target; and in panel B, the chip was hybridized to a mixture of the wild-type and mutant targets (SEQ. ID. Nos. 217-220).--

On page 11, lines 17-27, replace the paragraph with the following:

--Fig. 13, in sheets 1-3, corresponding to panels A, B, and C of Fig. 12, shows graphs of fluorescence intensity versus tiling position. The labels on the horizontal axis show the bases in the wild-type sequence corresponding to the position of substitution in the respective probes. Plotted are the intensities observed from the features (or synthesis sites) containing wild-type probes, the features containing the substitution probes that bound the most target ("called"), and the feature containing the substitution probes that bound the target with the second highest intensity of all the substitution probes ("2nd Highest"). The called sequences in A, B and C are (SEQ. ID. Nos. 221-223).--

On page 11, lines 28-33, replace the paragraph with the following:

--Fig. 14, in panels A (SEQ. ID. No. 226), B (SEQ. ID. Nos. 224,225), and C (SEQ. ID. No. 227), shows an image made from a region of a DNA chip containing CFTR exon 10 probes; in panel A, the chip was hybridized to the wt480 target; in panel C, the chip was hybridized to the mu480 target; and in panel B, the chip was hybridized to a mixture of the wild-type and mutant targets.--

On page 11, line 34 through page 12, line 6, replace the paragraph with the following:

--Fig. 15, in sheets 1-3, corresponding to panels A, B, and C of Fig. 14, shows graphs of fluorescence intensity versus tiling position. The labels on the horizontal axis show the bases in the wild-type sequence corresponding to the position of substitution in the respective probes. Plotted are the intensities observed from the features (or synthesis sites) containing wild-type probes, the features containing the substitution probes that bound the most target ("called"), and the feature containing the substitution probes that bound the target with the second highest intensity of all the substitution probes ("2nd Highest"). Called (SEQ. ID. Nos. 228-230).--

On page 12, lines 7-12, replace the paragraph with the following:

--Fig. 16, in panels A and B, shows an image made from a region of a DNA chip containing CFTR exon 10 probes; in panel A, the chip was hybridized to nucleic acid derived from the genomic DNA of an individual with wild-type ΔF508 sequences (SEQ. ID. No. 231); in panel B, the target nucleic acid originated from a heterozygous (with respect to the ΔF508 mutation) individual.--

On page 12, lines 13-23, replace the paragraph with the following:

--Fig. 17, in sheets 1 and 2 (SEQ. ID. No. 232), corresponding to panels A and B of Fig. 16, shows graphs of fluorescence intensity versus tiling position. The labels on the horizontal axis show the bases in the wild-type sequence corresponding to the position of substitution in the respective probes. Plotted are the intensities observed from the features (or synthesis sites) containing wild-type probes, the features containing the substitution probes that bound the most target ("called"), and the feature containing the substitution probes that bound the target with the second highest intensity of all the substitution probes ("2nd Highest").--

On page 12, lines 24-25, replace the paragraph with the following:

--Fig. 18 (SEQ. ID. Nos. 246-248): Image of the CFTR exon 11 tiled array hybridized with (A) wild-type and (B) mutant target.--

On page 12, lines 26 through page 13, line 5, replace the paragraph with the following:

--Fig. 19 (SEQ. ID. Nos. 249-250): Hybridization of R553X-Specific Array to Wildtype and Mutant Targets. Fig. 19A: Probe array specific for the R553X mutation. w = wild type probes, m = mutant probes, n = mutation position. Fig. 19B: fluorescence image of R553X array to wildtype target. Brightest signals correspond to shaded features in the "w" column (Fig. 19A), except in the "n" position where the probes complementary to C in both the "w" and "m" columns are bright. Fig. 19C: Fluorescence image of a R553X array to an R553X mutant target sequence. Signals correspond to shaded features in the "m" columns (Figure 19A), except in the "n" position where the probes complementary to T in both the "w" and "m" columns are bright. Fig. 19D: fluorescence image of a hybridization with both wild type and R553X mutant oligonucleotide targets. Brightest signals correspond to the full set of shaded features in Fig. 19A. Note that at the "n" position, the probes complementary to both C and T are bright in both the "w" and "m" columns.--

On page 43, lines 26-36, replace with the following:

--Pool 1 (SEQ. ID. Nos. 2-4): ATTGGMGAGTGCCC
=ATTGGaGAGTGCCC (complement to mutant 't')
+ATTGGcGAGTGCCC (complement to mutant 'g')

Pool 2 (SEQ. ID. Nos. 5-7): ATTGGKGAGTGCCC
=ATTGGgGAGTGCCC (complement to mutant 'c')
+ATTGGtGAGTGCCC (complement to wild type 'a')

Pool 3 (SEQ. ID. No. 8): ATTGGRGAGTGCCC
=ATTGGaGAGTGCCC (complement to mutant 't')
+ATTGGgGAGTGCCC (complement to mutant 'c')--

On page 44, lines 1-6, replace with the following:

		--Hybridization?		
Pool:		1	2	3
Target:	TAACCACTCACGGGAGCA	n	y	n
Mutant (SEQ. ID. No. 9):	TAACCcCTCACGGGAGCA	n	y	y
Mutant (SEQ. ID. No. 10):	TAACCgCTCACGGGAGCA	y	n	n
Mutant (SEQ. ID. No. 11):	TAACCtCTCACGGGAGCA	y	n	y--

On page 46, lines 28-29, replace with the following:

--Target (SEQ. ID. No. 12): ATTAACCACTCACGGGAGCTCT
Pool (SEQ. ID. No. 13): TGGTGNKYGCCCT --

On page 47, lines 1, replace with the following:

--The pooled probe actually comprises 16 individual probes (SEQ. ID. Nos. 14-29):--

On page 48, lines 12-17, replace with the following:

	--Target	
Wild:	ATTAACCACTCACGGGAGCTCT	(w)
Mutants (SEQ. ID. No. 30):	ATTAACCACTCcCGGGAGCTCT	(c)
Mutants (SEQ. ID. No. 31):	ATTAACCACTCgCGGGAGCTCT	(g)
Mutants (SEQ. ID. No. 32):	ATTAACCACTCtCGGGAGCTCT	(t)

TGGTGNKYGCCCT (pooled probe).--

On page 49, lines 3-10, replace the paragraph with the following:

--The above strategy of using pooled probes to analyze a single base in a target sequence can readily be extended to analyze any number of bases. At this point, the purpose of including three pooled positions within each probe will become apparent. In the example that follows, ten pools of probes (SEQ. ID. Nos. 33-41), each containing three pooled probe positions, can be used to analyze a each of a contiguous sequence of eight nucleotides in a target sequence.--

On page 49, lines 14-24, replace with the following:

--Pools:

4 TAATTNKYGAGTG - (SEQ. ID. No. 33)

5 AATTGNKRAGTGC - (SEQ. ID. No. 34)

6 ATTGGNKRGTGCC - (SEQ. ID. No. 35)

7 TTGGTNMRTGCCC - (SEQ. ID. No. 36)

8 TGGTGNKYGCCCT

9 GGTGANKRCCCTC - (SEQ. ID. No. 37)

10 GTGAGNKYCCTCG - (SEQ. ID. No. 38)

11 TGAGTNMYCTCGA - (SEQ. ID. No. 39)

12 GAGTGNMYTCGAG - (SEQ. ID. No. 40)

13 AGTGCNMYCGAGA - (SEQ. ID. No. 41)--

On page 51, lines 6-19, replace the paragraph with the following:

--To illustrate the loop strategy, consider a reference sequence of which the 4, 5, 6, 7 and 8th nucleotides (from the 3' termini are to be read. All of the four possible nucleotides at each of these positions can be read from comparison of hybridization intensities of five pooled probes (SEQ. ID. Nos. 42-46). Note that the pooled positions in the probes are different (for example in probe 55, the pooled positions are 4, 5 and 6 and in probe 56, 5, 6 and 7).

TAACCACTCACGGGAGCA Reference sequence

55 ATTNKYGAGTGCC - (SEQ. ID. No. 42)

56 ATTGNKRAGTGCC - (SEQ. ID. No. 43)

57 ATTGGNKRGTGCC - (SEQ. ID. No. 44)

58 ATTRGTNMGTGCC - (SEQ. ID. No. 45)

59 ATTKRTGNGTGCC - (SEQ. ID. No. 46)--

On page 52, lines 1-24, replace with the following:

		--Pools				
	Targets	55	56	57	58	59
Wild:	TAACCACTCACGGGAGCA	Y	Y	Y	Y	Y
Mutant (SEQ. ID. No. 47):	AgCACTCACGGGAGCA	Y	N	N	N	N
Mutant (SEQ. ID. No. 48):	AtCACTCACGGGAGCA	Y	N	N	Y	N
Mutant (SEQ. ID. No. 49):	TAAaCACTCACGGGAGCA	Y	N	N	N	Y
Mutant (SEQ. ID. No. 50):	TAACgACTCACGGGAGCA	N	Y	N	N	N
Mutant (SEQ. ID. No. 51):	TAACtACTCACGGGAGCA	N	Y	N	N	Y
Mutant (SEQ. ID. No. 52):	TAACaACTCACGGGAGCA	Y	Y	N	N	N
Mutant:	TAACCcCTCACGGGAGCA	N	Y	Y	N	N
Mutant:	TAACCgCTCACGGGAGCA	Y	N		N	N
Mutant:	TAACCtCTCACGGGAGCA	N	N	Y	N	N
Mutant (SEQ. ID. No. 53):	TAACCAgTCACGGGAGCA	N	N	N	Y	N
Mutant (SEQ. ID. No. 54):	TAACCAtTCACGGGAGCA	N	Y	N	Y	N
Mutant (SEQ. ID. No. 55):	TAACCAaTCACGGGAGCA	N	N	Y	Y	N
Mutant (SEQ. ID. No. 56):	TAACCACaCACGGGAGCA	N	N	N	N	Y
Mutant (SEQ. ID. No. 57):	TAACCACcCACGGGAGCA	N	N	Y	N	Y
Mutant (SEQ. ID. No. 58):	TAACCACgCACGGGAGCA	N	N	N	Y	Y--

On page 54, lines 8-14, replace with the following:

	--X	X	X	X - 4
Positions				
Target: TAAC	C=1111	A=1111	C=1111	T=1111
CACGGGAGCA (SEQ. ID. No. 59)				
	G=0001	C=0010	G=0011	A=0100
	T=0101	G=0110	T-0111	C=1000
	A=1001	T=1010	A=1011	G=1100--

On page 54, lines 29-31, replace with the following:

--First pooled probe

= ATTG [GCAT] T [GCAT] A GTGCCC

= ATTG N T N A GTGCCC (SEQ. ID. No. 60)--

On page 54, lines 39-43, replace with the following:

--Target:	TAACCACTCACGGGAGCA			
Pool 1(1) :	ATTGnTnAGTGCCC	=	16 probes	(4x1x4x1)
Pool 2(2) (SEQ. ID. No. 61):	ATTGGnnAGTGCCC	=	16 probes	(1x4x4x1)
Pool 3(4 (SEQ. ID. No. 62):	ATTGyrydGTGCCC	=	24 probes	(2x2x2x3)
Pool 4(8) (SEQ. ID. No. 63):	ATTGmwmbGTGCCC	=	24 probes	(2x2x2x3)--

On page 55, lines 41-42, replace with the following:

--Wild

Target (SEQ. ID. No. 1): TAACCACTCACGGGAGCA--

On page 56, line 4, replace with the following:

--Pool 5(c) (SEQ. ID. No. 64): ATTGdhsmGTGCCC = 36 probes (2x2x3x3)--

On page 57, lines 14-20, replace with the following:

--Reference (SEQ. ID. No. 65): 5' $T_{GGCTA}{}^{CGAGG}$AATCATCTGTTA

*

Probes (SEQ. ID. Nos. 66-69): 3' GCTCC CCGAT (Probe from first probe set)

3' GCACC CCGAT

3' GCCCC CCGAT

3' GCGCC CCGAT--

On page 59, lines 32-33, replace with the following:

--Reference (SEQ. ID. No. 70): . . . AGTACCAGATCTCTAA . . .

Probe set (SEQ. ID. No. 71): CATGGNC AGAGA (N = interrogation position).--

On page 65, lines 1 through page 66, line 8, replace Table 4 with the following:

Table 4

OLIGO NUMBER	SEQUENCE (SEQ. ID. Nos. 72-102)
787	TCTCCTTGGATATACTTGTGTGAATCAA
788	TCACCAGATTTCGTAGTCTTTTCATA
851	GTCTTGTGTTGAAATTCTCAGGGTAT
769	CTTGTACCAGCTCACTACCTAAT
887	ACCTGAGAAGATAGTAAGCTAGATGAA
888	AACTCCGCCTTTCCAGTTGTAT
934	TTAGTTTCTAGGGGTGGAAGATACA
935	TTAATGACACTGAAGATCACTGTTCTAT
789	CCATTCCAAGATCCCTGATATTTGAA
790	GCACATTTTTGCAAAGTTCATTAGA
891	TCATGGGCCATGTGCTTTTCAA
892	ACCTTCCAGCACTACAAACTAGAA

760	CAAGTGAATCCTGAGCGTGATTT
850	GGTAGTGTGAAGGGTTCATATGCATA
762	GATTACATTAGAAGGAAGATGTGCCTTT
763	ACATGAATGACATTTACAGCAAATGCTT
931	GTGACCATATTGTAATGCATGTAGTGA
932	ATGGTGAACATATTTCTCAAGAGGTAA
955	TGT CTC TGT AAA CTG ATG GCT AAC A
884	TCGTATAGAGTTGATTGGATTGAGAA
885	CCATTAACTTAATGTGGTCTCATCACAA
886	CTACCATAATGCTTGGGAGAAATGAA
782	TCAAAGAATGGCACCAGTGTGAAA
901	TGCTTAGCTAAAGTTAATGAGTTCAT
784	AATTGTGAAATTGTCTGCCATTCTTAA
785	GATTCACTTACTGAACACAGTCTAACAA
791	AGGCTTCTCAGTGATCTGTTG
792	GAATCATTCAGTGGGTATAAGCA
1013	GCCATGGTACCTATATGTCACAGAA
1012	TGCAGAGTAATATGAATTTCTTGAGTACA
766	GGGACTCCAAATATTGCTGTAGTAT
1065	GTACCTGTTGCTCCAGGTATGTT

On page 72, lines 3-12, replace the paragraph with the following:

--The sequences of several important probes are shown below (SEQ. ID. Nos. 103-111). In each case, the letter "X" stands for the interrogation position in a given column set, so each of the sequences actually represents four probes, with A, C, G, and T, respectively, taking the place of the "X." Sets of shorter probes derived from the sets shown below by removing up to five bases from the 5'-end of each probe and sets of longer probes made from this set by adding up to three bases from the exon 10 sequence to the 5'-end of each probe, are also useful and provided by the invention.--

On page 72, lines 23-31, replace the paragraph with the following:

--To demonstrate the ability of the chip to distinguish the ΔF508 mutation from the wild-type, two synthetic target nucleic acids were made. The first, a 39-mer complementary to a subsequence of exon 10 of the CFTR gene having the three bases involved in the ΔF508 mutation near its center, is called the "wild-type" or wt508 target, corresponds to positions 111-149 of the exon, and has the sequence shown below (SEQ. ID. No. 112):

5'-CATTAAAGAAAATATCATCTTTGGTGTTTCCTATGATGA.--

On page 72, line 32 through page 73, line-1, replace the paragraph with the following:

--The second, a 36-mer probe derived from the wild-type target by removing those same three bases, is called the "mutant" target or mu508 target and has the sequence shown below, first with dashes to indicate the deleted bases, and then without dashes but with one base underlined (to indicate the base detected by the T-lane probe, as discussed below) (SEQ. ID. No. 113):

5'-CATTAAAGAAAATATCAT---TGGTGTTTCCTATGATGA;

5'-CATTAAAGAAAATATCATTGGTGTTTCCTATGATGA.--

On page 74, lines 31-32, replace with the following:

--Target: 5'-CATTAAAGAAAATATCATTGGTGTTTCCTATGATGA

Probe (SEQ. ID. No. 114): 3'-TagTAGTAACCACAA--

On page 76, lines 1-3, replace with the following:

--5'-CCTTCAGAGGGTAAAATTAAG (SEQ. ID. No. 115) and the 21-mer probe mu480 to represent the mutant sequence:

5'-CCTTCAGAGTGTAAAATTAAG (SEQ. ID. No. 116).--

On page 77, lines 12-19, replace the paragraph with the following:

--To demonstrate clinical application of the DNA chips of the invention, the chips were used to study and detect mutations in nucleic acids from genomic samples. Genomic samples from a individual carrying only the wild-type gene and an individual heterozygous for ΔF508 were amplified by PCR using exon 10 primers containing the promoter for T7 RNA polymerase. Illustrative primers of the invention are shown below (SEQ. ID. Nos. 117-122).--

On page 82, lines 19-27, replace the paragraph with the following:

--The wild type oligonucleotide target (SEQ. ID. No. 233) (5'TGAGTGGAGGTCAACGAGCAAGA3') hybridizes to perfectly matched probes in five alternating columns (1, 3, 5, 7, 9) (Fig. 19B). The probes in the paired central columns, designated "n", interrogate the mutation position in the target. Because corresponding probes in these two columns are identical, hybridization results in a "doublet" in the center columns giving a total of six hybridized features for homozygous samples.--

On page 82, lines 37 through page 83, line 8, replace the paragraph with the following:

--Hybridization with the mutant oligonucleotide (SEQ. ID. No. 234) (5' TGAGTGGAGGTCAATGAGCAAGA 3') target shown in Fig. 19C has two key

differences from the wild type image in Fig. 19B. First, the hybridized features occur in probe columns offset by one (2, 4, 6, 8, 10) from those hybridized by the wild type target. Second, the central doublet occurs with the probes complementary to the mutant sequence (T), confirming the C to T base change in the mutant target. The relative fluorescence intensity range for perfect matches was 331-373 (mean = 351). The highest mismatch intensity range was 83-121 (mean = 96).--

On page 83, lines 26-31, replace the paragraph with the following:

--Fig. 20 shows hybridization of fluorescein-labeled, single-stranded DNA targets generated from two different mutant genomic DNA samples to mutation-specific probe arrays. One sample was compound heterozygous for G480C (GT) in exon 10 and G551D (GA) in exon 11. The other was homozygous for ΔF508. Wild type and mutant target sequences are as follows (SEQ. ID. Nos. 235-238):--

On page 84, lines 27-30, replace with the following:

--Wild Type (SEQ. ID. No. 239):	5' AAATATCATCTTTGGTGTT 3'
ΔF508:	5' AAATATCATcttTGGTGTT 3'
ΔF507:	5' AAATATcatCTTTGGTGTT 3'
F508C (SEQ. ID. No. 240):	5' AAATATCATCTGTGGTGTT 3'--

On page 85, line 37 through page 86, line 3, replace the paragraph with the following:

--Fig. 21 shows a typical image from this experiment made from CHO sample nine which had two exon 11 mutations, G542X and G551D. The mutation specific probe sets for these two mutations are indicated and the hybridization patterns are diagrammed. Wild type and mutant sequences are as follow (SEQ. ID. Nos. 241-244):--

On page 88, lines 6-34, replace the paragraph with the following:

--Conventional DNA sequencing technology is a laborious procedure requiring electrophoretic size separation of labeled DNA fragments. An alternative approach, termed Sequencing By Hybridization (SBH), has been proposed (Lysov et al., 1988, Dokl.Akad.Nauk SSSR 303:1508-1511; Bains et al., 1988, J. Theor.Biol. 135:303-307; and Drmanac et al., 1989, Genomics 4:114-128, incorporated herein by reference and discussed in Description of Related Art, supra). This method uses a set of short oligonucleotide probes of defined sequence to search for complementary sequences on a longer target strand of DNA. The hybridization pattern is used to reconstruct the target DNA sequence. It is envisioned that hybridization analysis of large numbers of probes can be used to sequence long stretches of DNA. In immediate applications of this methodology, a small number of probes can be used to interrogate local DNA sequence. The strategy of SBH can be illustrated by the following example. A 12-mer target DNA sequence, AGCCTAGCTGAA (SEQ. ID. No. 245), is mixed with a complete set of octanucleotide probes. If only perfect complementarity is considered, five of the 65,536 octamer probes -TCGGATCG, CGGATCGA, GGATCGAC, GATCGACT, and ATCGACTT will hybridize to the target. Alignment of the overlapping sequences from the hybridizing probes reconstructs the complement of the original 12-mer target:

TCGGATCG
CGGATCGA
GGATCGAC
GATCGACT
ATCGACTT
TCGGATCGACTT (SEQ. ID. No. 123)--

On page 100, lines 17-20, replace the paragraph with the following:

--The primers used to amplify the target nucleic acid should have promoter sequences if one desires to produce RNA from the amplified nucleic acid. Suitable promoter sequences are shown below (SEQ. ID. Nos. 124-127) and include:--

On page 106, line 1, Table 3 Heading, replace "Sequence Around Mutation Site" with the following:

--Sequence Around Mutation Site (SEQ. ID. Nos. 128-191)--

IN THE CLAIMS:

Claim 82 was amended as follows:

82. (Amended) A method of comparing a target nucleic acid with a reference sequence comprising a predetermined sequence of nucleotides, the method comprising:

(a) hybridizing a sample comprising the target nucleic acid to an array of oligonucleotide probes immobilized on a solid support, the array comprising:

(1) a first probe set comprising a plurality of probes, each probe exactly complementary to a subsequence of the reference sequence, the [segment] probe including at least one interrogation position complementary to a corresponding nucleotide in the reference sequence,

(2) a second probe set comprising a corresponding probe for each probe in the first probe set, the corresponding probe in the second probe set being identical to the corresponding probe from the first probe set that includes the at least one interrogation position, except that the at least one interrogation position is occupied by a different nucleotide in each of the two corresponding probes from the first and second probe sets;

wherein, the probes in the first probe set have at least three interrogation positions respectively corresponding to each of at least three contiguous nucleotides in the reference sequence, and

(b) detecting a hybridization pattern of the oligonucleotide probes to the target nucleic acid and determining from the hybridization pattern whether a nucleotide in the target sequence is the same or different from the corresponding nucleotide in the reference sequence.

Claim 88 was amended as follows:

88. (Amended) A method of comparing a target nucleic acid with a reference sequence comprising a predetermined sequence of nucleotides, the method comprising:

(a) hybridizing the target nucleic acid to an array of oligonucleotide probes immobilized on a solid support, the array comprising:

a perfectly matched probe exactly complementary to a subsequence of a reference sequence, the [segment] perfectly matched probe having a plurality of interrogation positions respectively corresponding to a plurality of nucleotides in the reference sequence,

for each interrogation position, three mismatched probes, each identical to the perfectly matched probe including the plurality of interrogation positions, except in the interrogation position, which is occupied by a different nucleotide in each of the three mismatched probes and the perfectly matched probe;

(b) for each interrogation position,

(1) comparing the relative specific binding of the three mismatched probes and the perfectly matched probe;

(2) assigning a nucleotide in the target sequence as the complement of the interrogation position of the probe having the greatest specific binding.

Claim 90 was amended as follows:

90. (Amended) A method of comparing a target nucleic acid with a reference sequence comprising a predetermined sequence of nucleotides, the method comprising:

hybridizing the target sequence to [the] an array [of claim 72] of oligonucleotide probes immobilized on a solid support, the array comprising at least one pair of first and second probe groups, each group comprising a first and second sets of oligonucleotide probes,

the first probe set comprising a plurality of probes, each probe exactly complementary to a subsequence of a reference sequence, the segment including at least one interrogation position complementary to a corresponding nucleotide in the reference sequence,

the second probe set comprising a corresponding probe for each probe in the first probe set, the corresponding probe in the second probe set being identical to the corresponding probe from the first probe set, except that the at least one interrogation position is occupied by a different nucleotide in each of the two corresponding probes from the first and second probe sets;

wherein the probes in the first probe set have at least three interrogation positions respectively corresponding to each of three contiguous nucleotides in the reference sequence;

wherein each probe in the first probe set from the first group is exactly complementary to a subsequence of a first reference sequence and each probe in the first probe set from the second group is exactly complementary to a subsequence from a second reference sequence;

determining which probes in the first group, relative to one another, hybridize to the target sequence, the relative specific binding of the probes

indicating whether the target sequence is the same or different from the first reference sequence;

determining which probes in the second group, relative to one another, hybridize to the target sequence, the relative specific binding of the probes indicating whether the target sequence is the same or different from the second reference sequence.

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#16

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT

Docket Number (Optional)
018547-004131US

In re Application of: Cronin et al.

Application No. 09/510,378

Filed: February 22, 2000

For: Arrays of Nucleic Acid Probes on Biological Chips

The owner*, Affymetrix, Inc. of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent Nos. 5,837,832; 6,027,880; and 6,309,823. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

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